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(54) Title: ODOR-MASKED AND STABILIZED COMPOSITIONS FOR TREATING KERATINOUS TISSUE, SKIN CONDITIONS, AND PROMOTING WOUND HEALING

(57) Abstract

This invention relates to odor-masked and storage stable compositions comprising film-forming proteins containing reducing agents and optionally at least one component selected from the following: reactive zinc salts, cationic polymers and cationic or nonionic surfactants. The present invention also relates to these compositions containing oxidizing agents and/or antioxidants and methods of use. The therapeutic compositions and methods of the present invention are particularly effective in promoting wound healing, and in inhibiting certain skin disorders, including eczema and seborrhea, scleroderma, hang nails, wrinkling and acne, including acne scarring. The therapeutic compositions and methods of the present invention have also shown enhanced effect as veterinary tools in reducing the debilitation associated with certain skin conditions in mammals including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitus ulcers and canine cutaneous granulomas ("lick" granuloma). The compositions of the present invention are also useful for conditioning horny keratinous tissue of mammals such as human hair and nails, and the hooves and fur of animals to improve their strength and appearance. In addition, these compositions are useful for promoting hair and nail growth.

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ODOR-MASKED AND STABILIZED COMPOSITIONS FOR TREATING KERATINOUS TISSUE, SKIN CONDITIONS, AND PROMOTING WOUND HEALING

SUMMARY OF THE INVENTION

This invention relates to novel compositions using film forming protein ingredients and includes reducing agents and optionally at least one of the following: reactive zinc salts, cationic polymers and/or cationic or nonionic surfactants. In addition, oxidizing agents and/or antioxidants are optionally included. The compositions of the present invention are particularly effective in promoting wound healing, the healing of abrasions and pressure sores, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, and in inhibiting certain skin disorders and treating abnormal conditions of the skin, including eczema and seborrhea, dandruff, psoriasis and other rash-like indications, scleroderma and acne. The compositions of the present invention further may be used to reduce scarring associated with severe forms of acne or wounds and to ameliorate wrinkling in skin due to exposure to the sun's rays or to aging. The therapeutic methods of the present invention are effective as veterinary tools in reducing the debilitation associated with certain skin conditions in mammals including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitis ulcers, and canine cutaneous granulomas ("lick" granuloma). The compositions of the present invention are also useful as cosmetic agents for conditioning horny keratinous tissue of mammals such as human hair and nails and the hooves and fur of animals to improve their strength and appearance. In addition, these compositions are useful for promoting hair and nail growth and for stabilizing the loss of hair in mammals, including humans.

It has now been discovered that compositions of the present invention which include film-forming protein compositions, reducing agents and optionally sufficient quantities of at least one or more of the following components: zinc salts, cationic polymers and cationic or non-ionic surfactants and also optionally include oxidizing agents and/or anti-oxidant compositions exhibit surprising activity for treating wounds, pyoderma, sebborhea, psoriasis, acn , miscellaneous rashes,

itching, callouses, corns, burns, eczematoid dermatitis, chronic dermatitis, decubitis ulcers, miscellan ous rashes, non-sp cific dermatitis and certain veterinary conditions including equine exuberant granuloma ("proud flesh") and canine cutaneous granulomas ("lick" granuloma). The compositions of the present invention may also be used to strengthen and improve the appearance and promote the growth of hair, nails, skin and other keratinous substrates and stabilize the loss of hair. The compositions of the present invention may also be used to prevent and promote the healing of hang nails.

The compositions of the present invention exhibit a substantial absence of odor which usually accompanies the storage of reducing agents and in certain cases, thiol-containing film-forming protein compositions. It is a particularly surprising result that compositions of the present invention may be formulated to substantially reduce the malodor associated with thiol-containing reducing agents and maintain the efficacy associated with a combination of a reducing agent and a film-forming protein. By substantially reducing the malodor associated with the storage of compositions comprising, in part, thiol-containing reducing agents and film-forming proteins, the compositions become pleasant to the smell and individuals are more inclined to use the compositions. In cases where the compositions are used therapeutically, patient compliance increases.

The essential ingredients of the compositions of this invention are the reducing agent and the film-forming protein, optionally at least one agent selected from among the following: zinc salts, cationic polymers and a cationic or nonionic surfactant is also included. In addition, the compositions of the present invention may also include an oxidizing agent and/or an antioxidant. Numerous additional components may also be included, for example water, bases, acids, buffering agents, emulsifying agents or surfactants, thickeners, preservatives, coloring agents and perfuming agents.

Background of the Invention

United States Patent 4,438,102 describes compositions which are useful for promoting the growth of normal dermal and epidermal tissue, and described as being us ful to promote w und healing in the soft k ratin tissue of the epidermis. Th compositions f the patent are described as containing

defined percentages of thioglycollic acid, ammonium hydroxide, glycerine, citric acid, hydrogen peroxide, gelatin, a lower alkanol, and a solvent such as acetone or diethyl ether. Several examples of wound healing are provided in th specification.

United States Patent 4,195,095 describes the use of certain formulations comprising thioglycollic acid for use in the treatment of fatty cysts, dandruff, scleroderma and other dermatological disorders, including acne vulgaris. Exemplary compositions comprise thioglycollic acid, hexachlorophene, sodium hydroxide, water and other ingredients, including bulking or gelling polymers and preservatives, among others.

U.S. Patent 3,842,848 describes a method of bonding especially prepared hydrolyzed peptide products of keratinaceous materials to human hair. The process is effected by conducting the reducing step of permanent waving in the presence of the peptide products and, thereafter, in a second step, oxidizing.

U.S. Patent No. 4,711,780 describes a medication for treating surface epithelium comprising ascorbic acid, a zinc salt a sulfur amino acid and optionally a mucopolysaccharide and/or a polysaccharide. Compositions of this patent are described as being useful for treating a number of infections and conditions, including wound healing.

G.B. Patent No. 2,160,419 describes a process for treating and improving the condition of keratinous tissue comprising no fewer than three steps: contacting the hair, skin or nails with a reducing composition, rinsing the treated tissue with water, contacting the rinsed tissue with an aqueous keratin protein hydrolysate and finally contacting the tissue with a neutralising composition containing an oxidizing agent.

Compositions which contain film-forming protein (preferably an activated thiol-containing film-forming protein) and a reducing agent in the absence of the sulfur stabilizing components of the present invention, although highly efficacious, tend to develop a pungent, malodor which in certain compositions may be quite unpleasant. In certain instances, such compositions, because of this malodor, may reduce the frequency with which an individual applies the composition.

It is therefore one object f the present invention to provide novel compositions and/or m thods for treating

keratinous tissue, for example, hair, skin and nails to make such tissue stronger and more pleasant in feel and appearance, hang nails, certain abnormal conditions of the skin including, for example, wounds, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, czematoid dermatitis, chronic dermatitis, decubitis ulcers, sebborhea, psoriasis, pyoderma, dandruff, itching, wrinkles, allergic skin reactions, miscellaneous rashes, acne and certain veterinary conditions including equine exuberant granuloma, and canine cutaneous granulomas ("lick" granuloma) utilizing compositions containing at least one film-forming protein in combination with a reducing agent which evidence or produce substantially no malodor or unpleasant smell even upon lengthy, i.e., at least about three months storage.

It is a further object of the present invention to provide non-malodorous storage stable, therapeutic compositions and methods for treating keratinous tissue, hang nails, and skin conditions as described above with compositions which do not evidence a malodor when stored over time and which are capable of maintaining the activity of an activated thiol-containing protein composition even when that composition contains an oxidizing agent.

It is a further object of the present invention to provide non-malodorous, storage stable compositions for treating chronic veterinary skin conditions which do not respond to traditional therapeutic methods, for example, equine exuberant granuloma ("proud flesh") and canine cutaneous granuloma ("lick" granuloma).

It is an additional object of the present invention to provide new compositions and methods for conditioning keratinous tissue including skin, nails and skin to enhance its strength, appearance and feel and promote hair growth and ameliorate the effects of wrinkling by exposing the tissue to activated protein and reducing agent optionally in the presence of at least one of following components: reactive zinc salts, cationic polymers and a surfactants selected from cationic and nonionic surfactants. This approach exhibits surprising efficacy in treating the above-mentioned skin conditions.

These and other objects of the present invention may be readily gleaned from the description of the invention that follows.

BRIEF DESCRIPTION OF THE INVENTION

The therapeutic compositions and methods of the present invention are useful for treating keratinous and related conditi ns, including wounds, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, seborrhea, psoriasis, dandruff, allergic skin reactions, acne, itching, callouses, corns, burns, abrasions, wrinkles, misc l-laneous rashes, non-specific dermatitis and certain veterinary conditions including eczematoid dermatitis, chronic dermatitis, equine exuberant granuloma ("proud flesh"), decubitis ulcers, and canine cutaneous granuloma ("lick" granuloma). In addition, the compositions and methods of the present invention may also be used to improve the strength, condition and appearance of hair, skin and nails, including split and cracked hair, nails and hooves, and for promoting the growth of hair and nails and preventing hair loss.

In using the present invention a composition comprising an activated protein, a compatible reducing agent, and optionally at least one of the following components: a reactive zinc salt, a cationic polymer and a surfactant selected from the group consisting of cationic and nonionic surfactants is contacted with an area of keratinous tissue affected with one of the above conditions. Further optionally, an oxidizing agent and/or an antioxidant may be included in the formulations of the present invention. The therapeutic compositions and methods of the present invention exhibit activity against non-healing skin conditions, especially canine cutaneous granulomas ("lick" granuloma) and equine exuberant granuloma ("proud flesh"). It is a particularly surprising result that certain compositions of the present invention are active in a broad range of applications without exhibiting the malodor associated with non-stabilized compositions or a substantial reduction in activity. Furthermore, the compositions of the present invention do not exhibit substantial "puckering" of packaging caused by compositions which do not contain at least one of the following: a reactive zinc salt, cationic polymer and cationic or nonionic surfactant.

Compositions useful in the therapeutic methods of the present invention include compositions having a pH of from about 3 to about 10, preferably a pH of about 4 to about 9. The pH of the compositi n depends upon the specific applica-

tion the composition is to be used for, and will vary within the above described pH ranges including a pH of 7.6 (physiological pH). Compositions of the present invention may comprise a reducing agent, a film-forming protein, preferably an activated film-forming protein, optionally in the presence of one or more of reactive zinc salts, cationic polymers and a surfactant selected from among cationic and nonionic surfactants in addition to other less essential components. An oxidizing agent and/or an antioxidant may also be included in the formulations.

It is preferred that the film-forming protein should be hydrated. A hydrated protein may be beneficial to certain types of skin conditions and wounds, especially burns, because the hydrated protein may be expected to provide additional moisture to the skin. The protein in the compositions of the present invention may react with and form chemical bonds with the keratin of human and animal skin, thus effecting an attachment of moist hydrated proteins to skin. The compositions are therefore useful for treating human and animal skin to chemically bond the activated protein to the skin, moisturize dry skin and provide a moisturizing vehicle to carry other agents into dehydrated skin. The protein in the compositions of the present invention may react with and form chemical bonds with the hard keratin of human and animal hair, nails and skin, thus effecting decreased hair breakage, increased hair thickness, increased nail hardness, decreased nail splitting and delamination and attachment of moist hydrated proteins to skin. The compositions of the present invention may also function as topical pharmaceutical carriers and vehicles.

The amount of film-forming protein that binds to skin will vary greatly as a function of the type of film-forming protein that is used. Protein that does not contain sufficient cysteinyl thiol groups does not bind to the keratinous substrate to the same extent or for the same duration of time as does protein containing sufficient cysteinyl thiol groups. Moreover, such a protein does not intercalate to become part of the natural skin as is the case of the protein keratin. In the case of activated protein, the percent of activated protein that bonds to the keratinous tissue will vary with the concentration of reducing agents in the composition and the number of activated thiol or mercapto groups in the activated

prot in and th keratinous tissue. The time that the reducing agent is in contact with the keratinous tissue is also important; the longer the keratinous tissue is in contact with the reducing agent, the greater will be the lik lihood of protein-keratinous tissue covalent bond formation.

The compositions of the present invention are preferably utilized at ambient temperatures, i.e., about 20°C to about 35°C; however, higher temperatures may be used, especially for treating the hair and nails of animals, including humans. Obviously, when treating a wound, especially a burn, treatment is kept to a lower temperature to avoid exacerbating the wound condition. Where the application of heat is viewed as advantageous, treating the keratinous substrate at higher temperatures is recommended. The keratinous tissue (hair and nails) may be treated over a period of time ranging from about 5 minutes to about 6 hours. The keratinous tissue may be treated acutely or chronically, with or without a dressing as needed. In certain embodiments, compositions useful in practicing the therapeutic methods of the present invention may be formulated with sustained or controlled release polymers to produce formulations capable of delivering active agent for extended periods of time. Reaction is effected by bringing the compositions of the present invention into contact with the keratinous substrate to be treated and allowing the treated tissue to dry. The time of contact may be varied at will.

In addition to the film-forming protein, compositions of the present invention also comprise at least one reducing agent, preferably a pharmaceutically compatible reducing agent. The reducing agent is preferably used in an amount sufficient to reduce the keratinous substrate to promote covalent binding of the film-forming protein. Although any reducing agent which is capable of producing free thiol groups from the disulfide bonds of cystine may be used in embodiments of the present invention, preferred reducing agents include pharmaceutically compatible thiol-containing reducing agents.

In addition to film-forming protein and reducing agent, the compositions preferably comprise at least one agent selected from among the following: reactive zinc salts, cationic polymers and surfactants sel cted from cationic and nonionic surfactants. When reactive zinc salts are used, they comprise a concentration effective for producing an odor-

masked, stable product which surprisingly maintains its broad range of activity. As used throughout the specification, a reactive zinc salt is any zinc salt which is soluble in the compositions of the present invention to the extent of at least about 0.05 weight percent. Preferred reactive zinc salts for use in the present invention include any zinc salt which is soluble in water or other carrier used to formulate compositions of the present invention. Although a number of zinc salts may be used either alone or in combination in the present invention, in general, the preferred zinc salts include those that are more readily soluble in water. Additional reactive zinc salts which may be used in the present invention include those that are only marginally soluble in water or other carrier, but increase markedly in solubility when formulated in compositions of the present invention. Such reactive zinc salts include zinc oxide (ZnO), among others. Generally, the amount of reactive zinc salt utilized ranges from about 0.05 weight percent up to the solubility limit of the zinc salt in water or other suitable carrier used. Preferably, at least about 0.19 weight percent of reactive zinc salt is used. A particularly preferred combination of zinc salts for use in the present invention includes zinc oxide and zinc sulfocarbolate^{tm} (zinc phenylsulfonate).

The amount of reactive zinc salt included within the compositions of the present invention generally ranges from about 0.05% by weight up to about 4% by weight of the compositions; however, those of ordinary skill will recognize that varying amounts of reactive zinc salt outside of this range may also be used depending up the effectivness of the particular salt chosen and the addition of cationic polymer and/or surfactant to compositions of the present invention. Those f ordinary skill will also recognize that the amount of reactive zinc salt to be used will also depend upon the type of zinc salt chosen and the amount of additional components, especially thiol-containing compounds which are present in the compositions of the present invention.

The compositions of the present invention may also includ at least one cationic polymer, either alone or in combination with one or more reactive zinc salts and/or a surfactant. The particular structure of the cationic polymer, while somewhat important to the overall efficacy of the cationic polymer, is only one of several factors which may determine

the effectiveness of cationic polymers of the present invention to stabilize the compositions of the present invention. It is also believed that the zinc and cationic p lymers or cationic and nonionic surfactants may complex with the thiol containing reducing agents and/or the proteins t stabilize these components from breakdown into malodorous side products.

Representative cationic polymers may contain nitrogen, phosphorous and sulfur cationic groups or mixtures of these cationic groups. Virtually any polymer containing cationic groups may be used in compositions of the present invention. Cationic polymers containing nitrogen and particularly quaternary ammonium groups are especially preferred.

It is preferred that the cationic polymers of the present invention are water soluble and contain quaternary-ammonium groups. Such polymers may be selected from among the quaternary nitrogen-containing cellulosic ethers, quaternary nitrogen-containing polysaccharides, graft copolymers of cellulose ethers and dialkyl diallyl ammonium halide polymers, copolymers of vinyl pyrrolidone and quaternized dialkylaminoalkyl methacrylate, copolymers of acrylamide and quaternized dialkyl amino dialkyl methacrylate as well as other polyquaternium polymers.

The cationic polymer is used in an amount effective to substantially reduce the malodor associated with the storage of thiol containing compositions, for example reducing agents and proteins which are included in the compositions of the present invention. In general, the cationic polymer used in the present invention comprises at least about 0.01 percent by weight to about 20 percent by weight, preferably about 0.025% to about 20% by weight and most preferably about 0.1% to about 5% by weight of the composition.

As stated hereinabove, the cationic polymer may be used alone or in combination with reactive zinc salts and/or surfactants. Where compositions are formulated using a cationic polymer in the presence of reactive zinc salts and/or pyrrolidone containing surfactants, the amount of cationic polymer, although generally falling within the weight ranges described hereinabove, may be reduced to accommodate the reactive zinc salt and/or surfactant chosen.

Compositions of the pr sent invention may also contain at least on surfactant selected from am ng cati nic and nonionic surfactants.

Among the cationic amin containing surfactants contemplated for use in the present invention include phenyl and alkyl ammonium surfactants, including benzalkonium bromide, benzethonium chloride, benzylhexadecyldimethylammonium chloride, and cetyltrimethylammonium bromide, among oth rs, oxyethyl substituted ammonium surfactants, including oxyethylammonium phosphate, ethoxylated alkylamines and the alkylimidazolines, Quaternary amine containing surfactants are clearly preferred including quaternized alkylamines, and quaternized ethoxylated alkylamines. Other cationic surfactants may also be used in compositions clearly contemplated by the present invention.

Compositions of the present invention may also contain at least one nonionic surfactant. Nonionic surfactants which are useful in the present invention include those surfactants which complex with mercaptides. Especially preferred nonionic surfactants for use in compositions of the present invention include, for example, those nonionic surfactants having cationic character.

Certain Compositions of the present invention preferably contain at least one pyrrolidone containing surfactant. As used herein, the term "pyrrolidone containing surfactant" is used to describe a chemical composition comprising a pyrrolidone ring to which is attached a hydrophobic group at the nitrogen position of the pyrrolidone ring which, together with the pyrrolidone ring, provides surfactant-like qualities. Although a number of hydrophobic groups may be employed, preferred hydrophobic groups include n-octyl, dodecyl and coco and tallow alkyl groups, most preferably n-octyl, attached to the nitrogen of the pyrrolidone ring. In the case of coco and tallow alkyl groups, these groups are represented by diversified alkyl substituents derived from cocoanut oil and tallow.

In certain aspects of the present invention, a chelating agent, for example, ethylenediaminetetraacetic acid (EDTA) or one of its chemical analogs, may be added to the composition in the presence of a reactive zinc salt to augment the scent-reducing capability. Such compositions may optionally contain a cationic polymer and/or a cationic or nonionic surfactant as described her in. Where EDTA is used in compositions of the present invention, it generally comprises between about 0.05 and about 2.0% by weight, preferably about 0.2 and

ab ut 0.9% by weight and most preferably between about 0.35 and 0.7% by weight of th composition.

In addition to the above-described components, compositions of the present invention may be formulated with an oxidizing agent, an antioxidant or mixtures f an oxidizing agent and an antioxidant. In addition, other components may also be added to the compositions of the present invention with or without the incusion of zinc salts, cationic polymers or nonionic and cationic surfactants including at least one or more of the following: acids, bases, buffering agents, emulsifying agents or additional surfactants, thickeners, preservatives, bulking agents, organic solvents, coloring agents and perfume agents. It is to be recognized by those of ordinary skill in the art that the choice of additives is made to avoid interactions with the active components of compositions of the present invention.

In certain embodiments of the present invention, depending upon the anti-oxidant used the reaction may be facilitated by heat. By removing the antioxidant in this manner, oxidation to promote covalent disulfide formation by the oxygen in ambient air may be promoted. Certain embodiments of the present invention may employ non-volatile oxidizing agents which may promote oxidation after the volatile antioxidants evaporate from the formulations.

In general, compositions of the present invention comprise about 0.1% to about 25% by weight of a film-forming protein, preferably an activated protein component, about 1.0% to about 15% by weight of a compatible reducing agent, preferably at least one agent selected from among reactive zinc salts, cationic polymers and cationic and nonionic surfactants, and at least one component selected from the group consisting of oxidizing agents, antioxidants, water, acids, bases, buffering agents, emulsifying agents or surfactants, thickeners, preservatives, organic solvents, chelating agents, film-forming polymers, coloring agents and perfuming agents.

Preferred compositions for use in the method aspects of the present invention are formulated to enhance the formation of free mercaptide or thiol groups in a thiol containing protein and the keratinous tissue to maximize the probability that a free thiol in the protein and a free thiol in the keratinous tissue will interact to form a covalent disulfide bond. The inclusion of an oxidizing agent in the same for-

mulation with or without an antioxidant may serve t promote covalent disulfide f rmation without having to res rt to a second oxidizing solution.

In addition to covalent disulfide bond formati n, a number of other mechanisms, including the film-forming characteristics of the protein may be responsible for the enhanced activity displayed by the therapeutic methods of the present invention. While not being bound by theory, in compositions utilizing a non-thiol containing protein, for example, gelatin or collagen, the film-forming characteristics of the protein may be the factor most responsible for enhanced activity.

The present invention utilizes compositions formulated as gels, creams, lotions, sprays or liquids of varying viscosities.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compositions comprising a film-forming protein, preferably an activated protein, a reducing agent and optionally at least one component selected from among the following: reactive zinc salts, cationic polymers and surfactants, including cationic and pyrrolidone containing surfactants. In addition, at least one component selected from among oxidizing agents, antioxidants, water, bases, acids, buffering agents, emulsifying agents or surfactants, thickeners, preservatives, organic solvents, coloring agents and perfuming agents may be included in the compositions of the present invention.

The protein used may be any film-forming protein. As used herein, a film-forming protein is any protein which forms a film on a keratinous substrate after being deposited. In these compositions, the film-forming protein is used in an amount effective to form a film on the keratinous substrate. Film-forming proteins for use in the present invention may include, for example, proteins which do not contain sufficient numbers of cysteinyl thiol groups to be capable of covalently bonding to a keratinous substrate. Proteins which do not contain significant cysteine but are film-forming proteins include collagen and gelatin, among others. Film-forming protein comprises about 0.1 to about 25.0% by weight f the composition, preferably about 1.0 to about 15.0% by weight for certain formulations and about 6 to about 10% by w ight for

other applications.

Film-forming proteins used in compositions employed in the present invention are exemplified by a number of proteins. Preferred proteins are those containing sufficient cysteine, i.e., at least about 1 cysteine amino acid for every 200 amino acids in a peptide chain (approximately, at least about 0.5% by weight cysteine, preferably, at least about 1.0% by weight cysteine, and most preferably at least about 5% by weight cysteine) to covalently bind to the keratinous tissue of hair, skin and nails to produce a durable permanent bond to keratinous tissue. By permanent bond we mean that the protein is not easily washed or rubbed off from the keratinous tissue and becomes as permanent as normal hair and nails.

A large number of exemplary film-forming proteins may be used in the present invention including gelatin, collagen, mucin, salmine, and sturine. Preferred proteins include keratin, food proteins, for example, casein, alpha and beta-lactalbumin, seed proteins, for example, soybean proteins, linseed protein, cotton seed protein, corn protein and peanut protein, among others, hemoglobin, insulin, myosin, zein, ovalbumin, hemoglobin, trypsin, chymotrypsin, chymotrypsinogen, elastases, thrombins, plasminogen, fibrinogen/fibrin, lysozyme, papain, serum albumin, heat coagulable mucoproteins isolated from cartilage, bones and skin, gamma globulin blood proteins, and a number of the blood factor proteins, including, for example, factor VIII, XII, IXa and Xa, among others. Of course, proteins which contain large numbers of cysteinyl residues are preferred, because these proteins would form the greatest number of covalent bonds with the keratinous tissue and thus, produce the greatest durability. The most preferred film-forming proteins for use in the present invention are those which contain sufficient cysteine to covalently bind to the keratinous substrate being treated.

Particularly preferred proteins for use in the present invention include proteins containing high percentages by weight of cysteine, for example, ribonuclease T1, human serum albumin and gamma globulins. An especially preferred protein for use in the present invention is keratin, because of its particularly high cysteine content (about 12% to about 17% by weight of cysteine) and because it is found in those substrates which are conditioned. In compositions to be used to treat certain wounds, exemplary compositions utilize keratin

ither alone or in combination with fibrinogen/fibrin or modified fibrinogen. Other compositions which may be us d to treat wounds may comprise fibrinogen/fibrin or modified fibrinogen alone.

Th activated prot ins used in the present invention, i.e. those proteins containing sufficient cysteinyl content to covalently bind to a keratinous substrate may be activated in the presence of reducing agent at a pH of about 9.0 or above for a time sufficient to produce free thiol group. This period is generally about 5 minutes up to about one hour. Activation periods of greater than one hour are less preferred because although such activation periods may marginally increase the amount of activated thiol groups in the protein, such periods may also result in hydrolysis of the protein int shorter, less advantageous peptide units.

A number of globular proteins contain cysteinyl residues within hydrophobic or other internal pockets of the protein structure. To activate these proteins and expose cysteinyl groups to the keratinous tissue, it may be advantageous to subject the proteins to denaturation and activation so that an activated cysteinyl residue of the denatured protein may be placed in proximity to the cysteinyl residues of the keratinous tissue to promote covalent binding.

The proteins of the present invention are preferably activated in the presence of reducing agent separately before they are formulated with the other components, because the addition of components other than a reducing agent at a pH above about 9.0 may adversely affect the rate at which cystinyl disulfide bonds in the protein are converted to cysteinyl mercaptide groups. This may lower the overall activity of the protein. However, although less preferred, it is possible to generate activated protein after formulation by simply exposing protein to reducing agents to a pH lower than 9.0 and even as low as pH about 4.0, provided that the cysteinyl content of the protein is sufficiently high to activate enough cysteinyl residues to promote covalent binding to the keratinous tissue.

The activated protein is preferably a keratin, but any protein which contains sufficient cysteinyl content to promote binding to activated keratinous tissue is contemplated for us in the present invention. Pref rred proteins are keratins because of their high cysteinyl content (generally, greater

than 10% by weight of the protein and often as high as 15-17% by weight of the protein) which may be obtained by hydrolysis of skin, feathers, wool and hair. A particularly preferred keratin is Keras 1^{tm} from Croda Chemicals International, Chesire, England. The molecular weight of proteins us ful in the present invention preferably varies between about 5,000 and 500,000 Daltons, and most preferably varies between about 120,000 and 130,000 Daltons.

Reducing agents which are useful in compositions of the present invention include sulfides, thiol-containing compositions including dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, thioalkanoic acid and mercaptocarboxylic acid analogues, for example, mercaptosuccinic acid, thiolactic acid and their pharmaceutically acceptable salts, among others, including thioglycollic acid and salts of thioglycollic acid. Preferred reducing agents for activating the protein are thioglycerol, cysteine, thiolactic acid and thioglycollic acid, and their pharmaceutically acceptable salts. Especially preferred reducing agents for use in the present invention include thioglycerol and salts of thioglycollic acid, especially ammonium thioglycollate. It is preferred that the reducing agent for activating the protein should be the same as the pharmaceutically compatible reducing agent which is used in the final formulation of the invention. The use of strong pharmaceutically incompatible reducing agents to activate the protein are less preferred and may make the use of the protein more difficult because the reducing agent may have to be removed from the activated protein before formulation.

In addition to a film-forming protein, compositions for use in the method of the present invention also contain a pharmaceutically compatible reducing agent in an amount equal to about 0.1 to about 15% by weight of the formulation. Preferred compositions contain about 0.5% to about 10% by weight, most preferably greater than about 1% by weight of a pharmaceutically compatible reducing agent. The amount of pharmaceutically compatible reducing agent varies according to the therapeutic or cosmetic use for which the compositions are intended, but generally falls within the range of about 0.1% t about 10% by w ight. A pharmaceutically compatible reducing agent is an agent which reduces cystinyl disulfide linkages in keratinous tissue to produce free thiol or mercap-

tide groups and is compatible with biological and/or pharmaceutical systems, especially for use on the skin, hair and nails of humans and/or the coats and hooves of animals. Pharmaceutically compatible reducing agents which are contemplated for use in the present invention include mercaptoethanol, dithiothreitol, thioglycerol, thiolactic acid, glutathione, cysteine and thioglycollic acid and its salts. An especially preferred reducing agent is ammonium thioglycollate.

Compositions of the present invention may additionally comprise at least one component selected from the following: reactive zinc salts, cationic polymers and cationic or nonionic surfactants. Generally, the reactive zinc salt is utilized in an amount effective to stabilize the compositions and prevent the formation of malodorous side products. In general, the reactive zinc salt is used in an amount ranging from about 0.05 to about the solubility limit of the zinc salt in water or other suitable carrier. Although the amount of zinc salt utilized may comprise as little as about 0.05 weight percent, an amount greater than 0.19 percent is preferred. Preferred zinc salts for use in the compositions of the present invention include highly water soluble organic and inorganic zinc salts including, for example, zinc acetate, zinc ammonium chloride, zinc bromide, zinc butyrate, zinc chlorate, zinc chloride, zinc fluoroborate, zinc formate, zinc formaldehyde sulfoxylate, zinc iodide, zinc lactate, zinc nitrate, zinc sulfocarbolate (zinc phenylsulfonate) and zinc sulfate, among others. Zinc salts of lower solubility includ zinc caproate, zinc carbonate, zinc fluoride, zinc iodate, zinc laurate, zinc oxalate, zinc oxide, zinc sulfite, zinc tartrate, zinc hydride, zinc cyanide dithiocarbamates (e.g., dimethyl), zinc phosphate, zinc potassium chromate and zinc tetraoxide chromate, among others. Especially preferred zinc salts include zinc oxide and zinc phenylsulfonate (zinc sulfocarbolate^{tm} available from Universal Preservachem, Inc., Brooklyn, New York, USA), used alone or in combination.

Compositions of the present invention may also include at least one cationic polymer, either alone or preferably in combinati n with a reactive zinc salt and/or cationic or nonionic surfactant. Virtually any cati nic polymer which stabilizes the compositions of the pr sent invention and inhibits the formation of malodorous gasses and other side products are

contemplated for use in the present invention. Such cationic polymers may be selected from among synth tic, semi-synthetic and natural cationic polymers. The cati nic polymers of the present invention may be selected from among polysaccharides, for example polycellulosic polymers, condensation polymers, polyamines, polyoxyalkylenes, polyalkyleneimines, homo and co-polymers of ethylenically unsaturated compounds, including poly(meth)acrylamides, poly(meth)acrylates, polyvinylpyrrol-lidones, diallyl dialkyl ammonium halides, as well as grafts or copolymers of such materials, among others, each of which contains cationic groups.

It is preferred that the cationic polymers of the present invention are water soluble and contain quaternary-ammonium groups. Exemplary preferred polymers may be selected from among the quaternary nitrogen-containing cellulosic ethers for example, JR-30M^{tm}, JR-125^{tm} and JR-400^{tm}, available from Amerchol Corp. New Jersey, USA, LR-400, LR-30M and SR-10, available from Union Carbide Corp., USA, quaternary nitrogen-containing polysaccharides, for example the Quatrisoft^{tm} polymers available from Union Carbide Corp., graft copolymers of cellulose ethers and dialkyl diallyl ammonium halide polymers, for example the Celquat^{tm} polymers, availabe from National Starch, New Jersey, USA, homo and copolymers of of dialkyl diallyl ammonium halide, for example the Merquat^{tm} polymers available from Calgon Corp., USA, copolymers of vinyl pyrrolidone and quaternized dialkylaminoalkyl methacrylate, for example, the Gafquat^{tm} polymers, available from GAF Corp., Linden, New Jersey USA, copolymers of acrylamide and quaternized dialkyl amino dialkyl methacrylate, for example, the Reten^{tm} polymers, available from Hercules, Inc., Wilming-ton, Del. USA as well as other polyquaternium polymers.

The cationic polymer is used in an amount effective to substantially reduce the malodor associated with the storage of thiol containing compositions, for example reducing agents and certain proteins which are included in the compositions of the present invention. In general, the cationic polymer is used in an amount comprising at least about 0.01 percent by weight to about 20 percent by weight, preferably about 0.025% to about 20% by weight and most preferably about 0.1% to about 5% by weight of the composition. S me cati nic polymers may produce irritation when placed in proximity to th skin. Those of ordinary skill in the art will understand to adjust

the amount and type of cationic polymer used in compositi ns of the present invention.

The cationic polymer may be used alone or preferably in combination with reactive zinc salts and/ r cationic or nonionic surfactants. Where compositions are formulat d using a cationic polymer in the presence of reactive zinc salts and/or cationic or nonionic surfactants, the amount of cationic polymer, although generally falling within the weight ranges described hereinabove, may be reduced to accommodate the zinc salt and/or surfactant.

Compositions of the present invention may also contain at least one surfactant selected from among cationic and nonionic surfactants. In general, surfactants may be added to the compositions to stabilize and prevent the formation of malodorous side products. Therefore, cationic and nonionic surfactants which tend to complex and stabilize mercaptides without reducing their activity are contemplated for use in the present invention. While any cationic surfactant which complexes and stabilizes mercaptides is contemplated for use in the present invention, it is preferred that cationic surfactants containing amines, and in particular, quaternary amines, are used in the present invention. In general, the surfactant comprises at least about 0.05% by weight of compositions of the present invention up to about 15% by weight of the compositions. Preferably, the surfactant comprises about 0.05% to about 5% by weight of the compositions of the present invention.

Among the cationic amine containing surfactants contemplated for use in the present invention include phenyl and alkyl ammonium surfactants, including benzalkonium bromide, benzethonium chloride, benzylhexadecyldimethylammonium chloride, and cetyltrimethylammonium bromide, among others, oxyethyl substituted ammonium surfactants, including oxyethylammonium phosphate, ethoxylated alkylamines, for example the Dehyquat^{tm} surfactants available from Henkel Corp., Ambler Pennsylvania and the alkylimidazolines, available from Mona Industries, Inc., West Paterson, New Jersey. Quaternary amine containing surfactants are clearly preferred including quaternized alkylamines, and quaternized ethoxylated alkylamines, the Monaquat^{tm} surfactants, available from Mona Industries, Inc., West Patterson, New J rsey. Oth r cationic surfactants may also be used in compositi ns clearly con-

templated by the present inventi n.

Compositions of th present invention may also contain at least one nonionic surfactant. Nonionic surfactants which are useful in the present invention include those surfactants which compl x with mercaptides. Especially preferred n nionic surfactants for use in compositions of the present invention include, for example, those nonionic surfactants having cationic character, i.e., exist as cations in certain resonance forms which may complex with mercaptides and stabilize the compositions of the present invention from producing malodorous side products. Preferred nonionic surfactants for use in the present invention include alkanolamide surfactants, Amide 6560^{tm}, available from Emery Corp., Mauldin, South Carolina, USA, ethoxylated alkanolamides, for example, ethoxylated taloamine, Trymeen^{tm} surfactant, available from Emery Corp., South Carolina and pyrrolidone containing surfactants. In addition to the above, certain fatty alcohol nonionic surfactants such as for example seteth and steareth alcohols may also be included in compositions of the present invention.

Compositions of the present invention most preferably contain at least one pyrrolidone containing surfactant in which a hydrophobic group is attached to the nitrogen of the pyrrolidone ring. Although a number of hydrophobic groups on the nitrogen of the pyrrolidone ring may be employed, preferred hydrophobic groups include n-octyl, dodecyl and coco and tallow alkyl groups, most preferably n-octyl, attached to the nitrogen of the pyrrolidone ring in the surfactants LP-100^{tm}, LP-300^{tm}, LP-800^{tm}, and LP-940^{tm}, available from GAF Corp., Linden, New Jersey USA. Generally, the compositions of the present invention contain about 0.05 to about 5% by weight of a pyrrolidone containing surfactant.

The presence of reactive zinc salts, cationic polymers and/or cationic and nonionic surfactants are used in amounts alone or in combination effective to stabilize the compositions of the present invention. By stabilizing the compositions of the present invention, the compositions do not exhibit appreciable malodor, precipitation or "puckering" of containers caused by reaction of the formulations with gasses present in the container.

In certain aspects f the pr sent invention, ethylenediamin tetraacetic acid (EDTA), for example Hampene 100^{tm}, available from Lowenstein, Inc., Brooklyn, New York,

USA, disodium, tetrasodium and zinc EDTA, or one of their chemical analogs, may be added to the composition in the presence of a reactive zinc salt. Such comp sitions may optionally contain a cationic polymer and/or a pyrrolidone containing surfactant as described herein. Where EDTA is used in compositions of the present invention, it generally comprises between about 0.05 and about 2.0% by weight, preferably about 0.2 and about 0.9% by weight and most preferably between about 0.35 and 0.7% by weight of the composition.

Compositions used in the present invention may additionally comprise an effective amount of an oxidizing agent, generally ranging from about 0.01 to about 4.0% by weight of the compositions. Preferred compositions comprise about 0.1 to about 1.5% of the oxidizing agent and most preferably about 0.5% to about 1.0% of the oxidizing agent. The oxidizing agent is included in compositions of the present invention to enhance oxidation which may promote the formation of covalent disulfide bonds between activated protein and keratinous tissue. Additionally, the oxidizing agent may function as a disinfecting agent to clean the keratinous tissue and enhance healing. Exemplary oxidizing agents include hydrogen peroxid (which may or may not be stabilized with, for example, urea) and its salts including ammonium sulfate peroxide, urea peroxide, pyrophosphate peroxide, carbonate peroxide, organic peroxides including acetyl peroxide, benzoyl peroxide, among others, alkali metal perborates including sodium perborate, the alkali metal bromates including sodium and potassium bromate and sodium and potassium iodate. In embodiments of the present invention which do not include an antioxidant, hydrogen peroxide is the preferred oxidizing agent. In the embodiments which include hydrogen peroxide, it is preferred that the amount of hydrogen peroxide should be included in an amount equal to about 0.01 to about 1.5% by weight of the composition and most preferably about 0.05 to about 1.0% by weight. Where oxidizing agents other than hydrogen peroxide are used, a higher percentage by weight is usually used compared to hydrogen peroxide which has a high oxidation equivalent per unit weight.

Of course, many of th th rapeutic and cosmetic compositions and methods do not requir the inclusion of an oxidizing ag nt, but it is often advantageous to include such an oxidizing agent. However, in certain compositions, it is

often advantageous to include an oxidizing agent, because the oxidizing agent may promote the polymerizati n of certain keratin molecules in situ, a c ndition which is advantageous for promoting the film-forming characteristics of certain thiol c ntaining pr teins.

Compositions of the present invention may also include an antioxidant instead of, or in addition to, an oxidizing agent in an amount equal to about 0.01 to about 2.0% by weight of the composition. In compositions comprising an antioxidant, the antioxidant is included to promote the storage stability of the formulations. Exemplary antioxidants may include alpha-tocopherol, hydroxyquinone, unipherol, tocopherol ascorbate, lecithin, chlorophyll, ascorbylpalmitate, linseed oil, tongue oil, other natural antioxidants such as the steam distillation extract of rosemary as disclosed in U.S. Patent No. 4,450,097, thiazoline carboxylate, dihydroquinolines, methyl gallate, propyl gallate, alkylaryl and diarylamines.

Certain chelating agents, for example, EDTA, may be employed to enhance the antioxidant effect of the above agents. It has also been found advantageous to add EDTA to the formulations containing a reactive zinc salt, as describ d hereinabove. The chelating agent may function to chelate any dissolved metals which may be responsible for the in situ generation of oxygen. Generally, the chelating agent comprises between about 0.05 to about 2.0% by weight of the formulation, preferably about 0.2 and about 0.9% by weight and most preferably about 0.35 to about 0.7% by weight of the composition.

In preferred embodiments of the present invention, when an oxidizing agent is not included in the formulations utilized, about 0.01% to about 2.0% of antioxidant is included in the formulations. Without the additional oxidizing agent, the antioxidant is included in compositions of the present invention to prevent atmospheric oxygen or oxygen dissolved in the solution from deactivating the protein or the reducing agent during storage. In compositions in which oxidizing agents are employed to promote the oxidation of free thiols r mercaptides to covalent disulfide bonds, the oxidizing agent comprises about 0.01% to about 4.0% by weight of an oxidizing agent and the antioxidant comprises about 0.01% to about 4.0% of the f rmulation.

As in the other compositions acc rding to the present invention, compositions comprising an antioxidant and optionally, an oxidizing agent, may additionally comprise acids, bases, buffering agents, emulsifying agents or surfactants, thickeners, chelating agents, film-f rming polymers, preservatives, organic solvents, coloring agents and perfume agents as described for other embodiments of the present invention. It is to be recognized by one of ordinary skill in the art that the choice of additives is made to avoid any interaction that may affect the activity of the the film-forming protein, reducing agent, and in certain cases, reactive zinc salt, cationic polymer, pyrrolidone containing surfactant, oxidizing agent or antioxidant.

It is often preferred to add a film-forming polymer to the compositions of the present invention to promote the film-forming effects of the proteins used in compositions of the present invention. Preferred film-forming polymers for use in the present invention include polyvinyl pyrrolidone, for example PVP K30 (GAF Charlotte, N.C.), carbomers, for example the Carbapol^{tm} polymers such as Carbapol 940^{tm}, polyacrylates, gums, for example, methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, propylcellulose and hydroxypropylcellulose, among other film-forming polymers.

Exemplary acids and bases are added to adjust the pH of the formulation to desired levels. Preferred acids include organic acids for example acetic acid, citric acid and tartaric acid, among others, and inorganic phosphoric acid including its salts such as the salts of mono- and di-hydrogen phosphoric acid. The inorganic phosphoric acid salts may also be included in the formulations as buffering agents. Preferred bases include organic amines, for example, monoethanolamine, triethanolamine, trimethylamine and triethylamine. Most preferred bases include ammonium hydroxide.

Buffering agents, for example the inorganic phosphoric acid salts indicated above, as well as other buffering agents, for example the salts of organic acids such as acetic acid and citric acid may be included in the formulations of the present invention in amounts ffective to maintain the pH of the formulation over tim . Pr ferably, the amount of buffering agent is included in an amount no greater than about 1.5% by weight of the f rmulation and most preferably is less than about

0.75% by weight. The pH of the formulation may be a factor in determining its stability and in maintaining the activity of certain components in the formulation, especially the activated protein and the compatible reducing agent. Thus, a buffering agent may be included within the formulation to maintain the pH at a relatively constant level over time.

To add homogeneity to and promote the solubility of the formulation, certain organic solvents may be included. Among the solvents that may be useful in certain embodiments of the present formulation are water soluble polar organic solvents, for example alkanols such as methanol, ethanol, propanol, butanol and carbonyl containing solvents for example acetone, butanone and the like, among others. Additional solvents include ethers and amines, for example diethyl or dipropyl ether and trimethyl or triethyl amine. Trimethylamine and triethylamine may also be added as bases.

The solvent added to the formulation may enhance the solubility of certain components. Where liquid formulations are contemplated, it is sometimes advisable to add an organic solvent to promote the solubility of certain less polar components, without which the compositions may separate into more than one phase. The addition of the organic solvent may produce a uniform, homogeneous single phase.

Emollients may also be included, especially in lotions to produce a uniform, homogeneous single phase and provide other favorable characteristics. An especially preferred emollient for use in formulations of the present invention is PPG 15-sterol ether which also may be added to the formulations of the present invention for its emulsifying characteristics.

An emulsifying agent or surfactant other than those surfactants, i.e., cationic and nonionic surfactants described hereinabove which are added in certain embodiemtns to stabilize the compositions and reduce the formation of malodorous side products, is often added to embodiments of the present invention to enhance the characteristics of the formulation, to promote the solubility of the protein and other components and the phase stability of the formulation. Such agents also provide detergent-like qualities to the formulations. Suitable surfactants or emulsifying agents may be nonionic, anionic or amphoteric. Of course, one of ordinary skill in the art will recognize that when combinations of surfactants

are to be used, the type and amount of surfactants must be adjusted to maintain the stability of th emulsion. Nonionic emulsifying compositions include, for example the low r alkyl ne oxide condensati n products of hydrophobic compounds, for example ethylene oxide condensation products with higher fatty acids, higher fatty alcohols or alkylated aromatic hydrocarbons and higher molecular weight polypropylene glycols. Preferred nonionic emulsifying compositions include polyoxyethylene ethers including polyoxyethyleneisohexadecyl ether, for example Arlasolve 200^{tm} (available from ICI Americas, Wilmington Delaware), polyoxyethylenelauryl ether, for example Brij 35^{tm} (ICI), polyoxyethylenestearyl ether, for example Brij 72^{tm}, and Brij 78^{tm} (ICI) and polyoxypropylenestearyl ether, for example PPG-15 stearyl ether (Arlamol E, ICI). Other exemplary emulsifiers includ ethoxylated lanolin, for example, Lanogel 41^{tm} (Amerchol, Inc., Edison, N.J.). Exemplary anionic surfactants include sulfuric acid esters of polyhydric alcohols, e.g. lauryl sulfate, cetyl sulfate, etc., higher fatty alcohol sulfates derived from coconut oil, hydroxy sulfonated higher fatty acid esters such as, e.g., higher fatty acid esters of 2,3-dihydroxy-propane sulfonic acid, higher fatty acid esters of low molecular weight alkylol sulfonic acids, e.g., oleic acid ester of isethionic acid, sulfated higher fatty acid alkylolamides such as e.g., ethanolamide sulfates, higher fatty acid amides of amine alkyl sulfonic acids, e.g., lauric amide of taurine, among others, and aromatic containing anionic synthetic surfactants. Exemplary amphoteric surfactants include the salts of N-alkyl compounds of betaamino propionic acid wherein the alkyl group is derived from a fatty acid such as a mixture of coconut oil fatty acids, among others.

In certain embodiments of the present invention, it may be preferable to add an anti-foaming agent to certain compositions to promote homogeneity and prevent foaming from surfactant action. A preferred anti-foaming agent for use in embodiments of the present invention includes, for example, Dimethicone^{tm}, available from Dow Chemical Corp., Midland, Michigan.

Thickeners or g lling agents may be added to provid additional w ight and a more viscous feel to the formulations or, in certain cases, to provide additional film-forming char-

acteristics to the compositions of the present invention. Suitable thickening agents include polyvinyl pyrollidone, f r example PVP K30 (GAF Charl tte, N.C.) polyacrylat s, carbomers, for example carboxyvinyl polymer such as Carbapol 940 (available from B.F. Goodrich, Cleveland, Ohio) polyoxyethylene stearyl ethers, for example, polyoxyethylene-2 stearyl ether such as Steareth 2^{tm} (ICI) and polyoxyethylene-20 stearyl ether such as Steareth 20^{tm} (ICI), sodium alginate, carageenan, agar, ethoxylated polyvinyl alcohol, gums, for example methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, propylcellulose and hydroxypropylcellulose, acacia, tragacanth, guar, and quince, among others. In compositions which are contemplated to be formulated as a gel or lotion, Isoseteth 20^{tm} (polyoxyethyleneisohexadecyl ether, ICI), and Steareth 2^{tm} and 20^{tm} are preferred for use as thickening agents. In compositions which are contemplated to be formulated as creams, preferred thickeners include Steareth 2^{tm} and Steareth 20^{tm} and the carbomer polymers, for example Carbapol 940^{tm}.

Preservatives are added for preventing microbial growth in the presence of protein nutrients. Exemplary preservatives include benzoic acid analogs including, among others, sodium benzoate. Other presevatives include propyl and methyl paraben, Dowicil^{tm} (Dow Chemical Corp., Midland, Mi.) and formaldehyde solution. An especially preferred preservative is Germaben II^{tm}, available from Sutton Laboratories, New Jersey.

Other agents may also be added to certain embodiments of the present invention which are intended to treat wounds for the purpose of disinfecting the wounds and surrounding tissue and for providing antimicrobial protection. Among the preferred agents for this use include the topical disinfectants and antiseptics, for example, Benzalkonium chloride, cetrimide, chloramine, chlorhexidine, among others. Antimicrobial agents which may be used in the present invention include neomycin, bacitracin, spectinomycin, sulfa containing preparations, and polymixin, among others, and antifugal agents such as griseofulvin, amphotericin, chlordantoin, clotrimazole, dimethizole, miconazole and nystatin, among others.

Coloring agents and perfume agents may also be add d to enhance the characteristics of the formulations.

In addition to a large number f cosmetic and therapeutic uses, compositions of the present invention may be used to treat acne. Compositions for treating acne may include the compositions of the present invention in combination with pharmaceutically effective amounts of benzoyl peroxide, tetracycline and other anti-acne agents. The compositions of the present invention may also be used to resolve pock marks and acne scars in individuals who have not had acne for years. Compositions of the present invention may also b used to ameliorate wrinkling of skin that occurs with age or with overexposure to the sun and to grow hair and nails and prevent hair loss.

Compositions of the present invention may also be used to treat dandruff. Certain compositions for treating dandruff may include the compositions of the present invention in combination with an effective amount of a traditional anti-dandruff agent, for example, zinc pyrithione.

The compositions of the present invention are applied as a liquid, cream, gel or lotion by rubbing an effective amount of the compositions into the keratinous tissue to be treated. Generally, the composition is used in an amount effective to produce a thin film over the treated area. Following application, the compounds are allowed to dry. In certain cases, drying may be accelerated by the use of heat or circulating air. Subsequent to drying, formulations may be washed off, although this is not preferred when the compositions are used to treat wounds. When treating dandruff or sebborhea, the compositions may be washed before drying.

The method aspects of the present invention comprise exposing the area of keratinous tissue to be treated to any one of the compositions previously described hereinabove. Depending on the type of skin condition to be treated or the cosmetic effect desired in hair, skin or nails, the compositions of the present invention may be applied to the affected area at least once a day and as many times a day as is necessary to produce an improved condition. Generally, the therapeutic compositions are applied to the affected area between one and four times a day. Applications of fewer than on p r day may be performed depending upon the use, indicati n and severity, specially in the cosmetic area. For example, in the treatment of dandruff, sebborhea and skin conditions other than wounds, the formulation need only be applied

after or during shampooing, which may only be once or twice a week. The duration of therapy will depend on the condition treated and on the response of the condition to the therapy. Thus, when chronic conditions that do no respond to traditional therapy are being treated, it is to be expected that the duration of therapy will be longer than when less severe conditions are treated.

In producing the compositions of the present invention, a number of methods may be employed. However, a preferred method of producing the compositions involves first activating proteins containing sufficient cysteinyl groups and then stabilizing the activated proteins in the presence of one or more of a reactive zinc salt, a cationic polymer or a surfactant selected from cationic and nonionic surfactants effective to substantially reduce the formation of malodorous side products.

The method involves activating a protein containing cysteinyl groups in the presence of a reducing agent, as described herein, preferably, at a pH above about 9.0 to produce a protein wherein a number of the thiol groups are reduced, i.e., the thiols exist as mercaptides (cysteinyl groups), not dithiols (cystinyl groups). After the activation step, an effective amount of one or more of the reactive zinc salts, cationic polymers and surfactants selected from among cationic and nonion surfactants is combined with the reducing agent, the activated protein and other components. In the case of reactive zinc salts, it has surprisingly been discovered that certain zinc salts, for example ZnO, which are often quite insoluble in water (the solubility of ZnO in water, for example is 0.00016 g/ 100cc) or other carrier used to formulate the compositions of the present invention will dissolv into the water or other carrier to a much greater extent than would otherwise occur in the absence of protein and reducing agent.

Of course, it is also possible to produce the compositions of the present invention by simply mixing the components without regard to timing or activation of the protein component. This method may be useful for producing the compositions of the present invention when the protein is a film-forming protein which contains insufficient cysteinyl groups, i.e., too few cysteinyl groups to covalently bind to th keratinous substrate to produce covalent bonding of protein to

substrate, for example dible gelatin or collagen. However, even where such film-forming proteins ar utilized, in certain formulations it may be advantageous to formulate such compositions in th pr s nce of a reducing agent at a pH above about 9.0 t facilitate th amount of reactiv zinc salt which can be dissolved into the compositions.

Although not to be bound by theory, it is believed that the surprising therapeutic activity exhibited by compositions useful in the present invention may be the result of a combination of pharmacological effects which have been maintained through the use of the stabilized products of the present invention. Given the biological source of the protein and the reactive nature of the medium in which it is included, the possibility for the formation of biologically reactive products must be considered. These biological products may contribute to the biological effects of many possible mechanisms of action, including; moisturization of the affected area by hydrated protein, film formation, cytoskeletal interaction and mediation of the clotting process, disulfide covalent bond formation with the keratinous substrate resulting in the production of a "natural bandage" effect, the release of endogenous mediators of skin function (e.g. fibronectin, kinins and prostanoids), receptor modification and vasodilation. It is a surprising result that compositions of the present invention maintain substantially the same activity as the compositions described, in, for example, U.S. Patent Application Serial Number 319,402, entitled "Compositions and Methods for Treating Skin Conditions and Promoting Wound Healing", filed March 3, 1989 and U.S. Patent Application Serial Number 319,147, entitled "Storage Stable Compositions and Methods for Treating Keratinous Tissue", filed March 3, 1989, relevant portions of which are incorporated by reference herein, without evidencing instability and the production of malodorous side products.

The following examples are provided to illustrate the present invention and should not be construed to limit the scope of the invention of the present application in any way.

EXAMPLE 1

PHASE	INGREDIENT	PERCENT BY WEIGHT
A.1	DEIONIZED WATER	61.90
B.1	PROPYLENE GLYCOL	0.15
B.2	LANOGEL 41	0.15
B.3	BRIJ 35	0.41
B.4	PVP-K30 (25% SOLN)	0.70
C.1	GLYCERINE	0.50
C.2	CITRIC ACID (5.88% SOLN)	0.14
C.3	HYDROGEN PEROXIDE (3% SOLN)	1.61
C.4	ACETONE	0.41
C.5	ISOPROPANOL (99% SOLN)	1.20
C.6	KERASOL	5.87
D.1	GERMABEN II	2.93
E.1	AMMONIUM THIOGLYCOLLATE (60% SOLN) (previously adjusted to pH=9 with NH3)	10.34
E.2	DEIONIZED WATER	8.55
E.3	KERASOL	2.95
F.1	HAMPENE 100 (EDTA)	0.58
G.1	ZINC OXIDE	1.47
H.2	ZINC SULFOCARBOLATE	0.29
	TOTAL PERCENTAGE	=100.00

PROCEDURE:

In general, all metal (in machinery, containers or otherwise) coming into contact with this formulation at any time must be thoroughly "pickled", i.e. treated with industrial grade nitric acid (about 1N) to avoid any metal oxide effect on the reducing agent during formulation.

1. Heat phase A to 100° F.
2. Combine phase B ingredients separately heating at about 125°F until B.3 is melted. Mix thoroughly, then add to phase A at 100° for 10 minutes.
3. Premix the ingredients in phase C in the order listed while mixing continuously. Add phase C to phases A & B, still at 100°, and mix for 10 minutes.
4. Add phase D to phases ABC while mixing, and mix for another 10 minutes. The batch may become cloudy at this point, but this is normal.
5. Combine the ingredients in phas E in the order listed, and mix f r 10 minutes. This step is designed to activate the Kerasol. Add phase E to phases ABCD while mixing and con-

tinue to mix for 10 minutes. Th batch becomes a clear liquid.

6. While continuing to mix, add phase F to the batch and mix for 10 minutes.

7. Increase mixing to high speed and create a vortex (if possible). Slowly add phase G then phase H to the batch directly into the vortex. Mix until these powders are completely dissolved. Depending upon the efficiency of the mixing procedure this could take up to 30 minutes.

8. The final pH of this formulation ranges between about 8.0 and 8.2.

EXAMPLE 2

PHASE	INGREDIENT	PERCENTAGE
A.1	CONCENTRATED STOCK SOL'N FROM EXAMPLE 1	34.11
A.2	DEIONIZED WATER	60.33
B.1	ARLASOLVE 200^{tm}	4.00
C.1	SURFIDONE LP-100^{tm}	0.66
C.2	SCENT	0.90
	TOTAL PERCENTAGE	= 100.00

PROCEDURE

1. Combine ingredients in phase A, then place phase B in a separate container and heat to 145°-150° F., and maintain at that temperature.

2. Combine C.1 and C.2, mix well, and allow to stand for 5 minutes, then add to phase B and mix mechanically for another 5 minutes.

3. While mixing phase A, add the combined phases B and C to phase A. The result must be a clear liquid with a pH of about 8.1.

EXAMPLE 3

PHASE	INGREDIENT	PERCENTAGE
A.1	Arlamol E^{tm}	1.36
.2	Brij 72^{tm}	5.21
.3	Mineral Oil 70	11.60
.4	Propylparaben	0.18
B.1	Purified Water	77.4
.2	Disodium EDTA	0.10
.3	Dimethicone^{tm}	0.09
.4	Methylparaben	0.41
.5	Propylene Glycol	1.36
C.1	Dowicil 200^{tm}	0.05
.2	Purified Water	0.50
D.1	Formaldehyde 37%	0.2
E.1	Germaben II^{tm}	0.23

PROCEDURE:

1. Heat A phase components to 70-75°C and mix until uniform.
2. Charge main kettle with water and begin heating to 70-75°C.
3. Add the remainder of phase B components and mix to dissolve the solids.
4. Add, at 70-75°C, A phase to B phase while mixing. Blend well and cool to 35-40°C.
5. Premix C phase and add to the batch when the solution is clear. Add D and E phases one at a time and mix in well.
6. Cool to 25-30°C and use at this temperature.

EXAMPLE 4

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.15
B.1	CARBOPOL 940tm	1.60
C.1	GERMABEN IItm	0.40
D.1	LOTION FROM EXAMPLE 3	8.70
E.1	TRIETHANOLAMINE (99% SOLN)	1.43
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100	0.65
G.2	SCENT	0.87
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. Place phase A in a high speed mixer, create a vortex, sprinkle phase B into vortex, and mix until completely and thoroughly blended.
2. Add phas C to phases AB while mixing, and mix until uniform.
3. Premix phase D. Add phase D to phases ABC, and mix until completely uniform.
4. Add phase E to phases ABCD. This causes the batch to gel. Mix until completely uniform.
5. Premix phase F, and add to a separate container sufficient to hold phases F and G.
6. Premix phase G, mix well and allow to stand for 5 minutes. Add phase G to phase F and mix mechanically for 10 minutes. Keep mixing and add phases FG to phases ABCD while mixing. Continue mixing until smooth and uniform.
7. Final pH is about 5.85.

EXAMPLE 5

PHASE	INGREDIENT	PERCENTAGE
A.1	CONCENTRATED STOCK SOLN FROM EXAMPLE 1	91.42
B.1	ARLASOLVE 200^{tm}	5.9
C.1	SURFIDONE LP-100^{tm}	1.78
C.2	SCENT	0.9
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. After phase A has been prepared, place phase B in a separate container and heat to 145°-150° F., and maintain at that temperature.
2. Combine C.1 and C.2, mix well, and allow to stand for 5 minutes, then add to phase B and mix mechanically for another 5 minutes.
3. While mixing phase A, add the combined phases B and C to phase A. The result is a clear liquid with a pH of about 8.1.

EXAMPLE 6

PHASE	INGREDIENT	PERCENTAGE
A.1	Arlamol E™	2.33
.2	Brij 72™	8.93
.3	Brij 78™	2.25
.4	Mineral Oil 70	19.89
.5	Propylparaben	0.31
B.1	Purified Water	62.15
.2	Disodium EDTA	0.16
.3	Dimethicone™	0.16
.4	Methylparaben	0.70
	Propylene Glycol	2.33
C.1	Germaben II™	0.79

Procedure

1. Charge main mixing kettle with B ingredients and heat while mixing to 80-85°C.
2. In a separate container heat A ingredients to 80-85°C and mix until uniform.
3. At 80-85°C, add mixed A ingredients to mixed B ingredients while thoroughly mixing.
4. Cool mixture of A and B to 50-55°C. At 50-55°C, add Germaben (C) and blend in very well. Continue to cool to 30°C and use at this temperature.

EXAMPLE 7

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.30
B.1	CARBOPOL 940™	2.38
C.1	GERMABEN II™	0.59
D.1	LOTION FROM EXAMPLE 6	8.90
E.1	TRIETHANOLAMINE (99% SOLN)	0.25
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100™	0.50
G.2	SCENT	0.88
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. Place phase A in a high sp ed mixer, create a vortex, sprinkle phase B into vortex, and mix until completely and thoroughly blend d.
2. Add phas C to phases AB while mixing, and mix until uniform.
3. Premix phase D. Add phase D to phases ABC, and mix until completely uniform.
4. Add phase E to phases ABCD. This causes the batch to gel. Mix until completely uniform.
5. Premix phase F, and add to a separate container sufficient to hold phases F and G.
6. Premix phase G, mix well and allow to stand for 5 minutes. Add phase G to phase F and mix mechanically for 10 minutes.
   Keep mixing and add phases FG to phases ABCD while mixing. Continue mixing until smooth and uniform.
7. Final pH is about 5.4.

EXAMPLE 8

PHASE	INGREDIENT	PERCENTAGE
A.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	34.11
A.2	DEIONIZED WATER	60.75
B.1	ARLASOLVE 200™	4.00
C.1	SURFIDONE LP-100™	0.66
C.2	SCENT	0.48
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. Combine ingredients in phase A, then place phase B in a separate container and heat to 145°-150°F., and maintain at that temperature.
2. Combine C.1 and C.2, mix well, and allow to stand for 5 minutes, then add to phase B and mix mechanically, for another 5 minutes.
3. While mixing phase A, add the combined phases B and C to phase A. The result must be a clear liquid with a pH of about 8.1.

EXAMPLE 9

PHASE	INGREDIENT	PERCENTAGE
A.1	DEIONIZED WATER	56.35
B.1	CARBOPOL 940tm	1.60
C.1	GERMABEN IItm	0.40
D.1	LOTION FROM EXAMPLE 3	8.70
E.1	TRIETHANOLAMINE (99% SOLN)	1.43
F.1	CONCENTRATED STOCK SOLUTION FROM EXAMPLE 1	30.20
G.1	SURFIDONE LP-100tm	0.45
G.2	SCENT	0.87
	TOTAL PERCENTAGE	100.00

PROCEDURE

1. Place phase A in a high speed mixer, create a vortex, sprinkle phase B into vortex, and mix until completely and thoroughly blended.
2. Add phase C to phases AB while mixing, and mix until uniform.
3. Premix phase D. Add phase D to phases ABC, and mix until completely uniform.
4. Add phase E to phases ABCD. This causes the batch to gel.
   Mix until completely uniform.
5. Premix phase F, and add to a separate container sufficient to hold phases F and G.
6. Premix phase G, mix well and allow to stand for 5 minutes.
   Add phase G to phase F and mix mechanically for 10 minutes.
   Keep mixing and add phases FG to phases ABCD while mixing.
   Continue mixing until smooth and uniform.
7. Final pH is about 5.85.

EXAMPLES 10-16

FORMULATIONS CONTAINING CATIONIC POLYMERS

To the concentrated liquid of example 11 is added 0.5, 1, 2, 3, 4, 5 and 6% by weight of cationic polymer JR-400. All samples proved to be active; there was a dose related decrease in malodorous thiol or sulfide scents across the range tested. The formulations containing 5 and 6% JR-400 were too viscous to be desirable as therapeutic liquids. Liquids containing 4% JR-400 were highly desirable in terms of viscosity and optimal scent profile.

EXAMPLES 17-18
FORMULATIONS CONTAINING CATIONIC POLYMERS AND ZINC AND NONIONIC SURFACTANTS

To Concentrated Stock Solution (Example 1) was added 0.45% Surfidone LP-100 until the mixture was thoroughly homogenized. This produced a composition which produced a further reduction in scent but maintained efficacy (See similar example 2). To this zinc/surfidone mixture was added JR-400 up to about 4% by weight of the composition. This pr - duced a composition which provided a further reduction in scent and a useful, efficacious composition. An excessive surfactant effect became manifest as an inhomogeneity in the formulations such that thinner and thicker areas of the formulation were observed. Results of this composition indicated that scent was reduced and the composition was useful.

TREATMENT EXAMPLES
EXAMPLES 19-23

A horse with a bilateral saddle rub, which made it impossible to ride the horse, was treated with the formulation from example 4. Within 1 day the soreness was gone enabling the horse to be ridden. Within 3 days new hair growth was visible, and within 2.5 weeks the site was indistinguishable from the rest of the coat.

A 33 year old woman used the formulation from example 7 on her fingernails for 2 weeks and observed a dramatic increas in hardness and rate of growth.

The 8 year old daughter of the above woman, who was prone to hang nails, and consistently had multiple hang nails on ach finger, was treated with formulati n from example 7. Within 2 days th discomfort of the hang nails disappeared. Within a week there was a marked decreas in the obs rvable hang nails. Within 2 weeks only one hang nail was observable. The mother could not recall when her daughter only had one hang nail.

A boxer dog which had idiosyncratically licked its forepaws since birth 4 years ago was treated with the formulation from Example 10. Previous treatments which utilized antibiotics, steroid hormones, antihistamines, and other foul tasting compositions had all been unsuccessful. Within 30 minutes after the first application, the licking behavior ceased. When treated with this formulation the licking behavior is consistently absent. When it reoccurs, a repeat application effectively stops the licking within 5 minutes.

A 15 month old child with a moderate-severe diaper rash was treated once, overnight, with the formulation from example 7. In the morning the rash was approximately 85% gone. The parents, who had other children, and had suffered similar episodes of diaper rash previously, were amazed at the response.

The invention has been described in such manner as to enable those skilled in the art to understand and practice it, preferred embodiments having been fully identified. It is to be understood, however, that the foregoing examples have been set forth in great detail but should not be viewed as limiting the present invention in any way.

EXAMPLE 24
SCENT REDUCTION

Formulations which did not contain a reactive zinc salt, a cationic polymer or a cationic or nonionic surfactant evidenced a malodor which necessitated considerable scenting with heavy, cloying fragrances. The scents used to cover the malodor w re not ideal, because of the heavy fragrance and the n ed to use high concentrations. Although an improvement over unscented compositi ns, they were not extremely pleasing and

evidenced some instability. Comp sitions utilizing a reactive zinc salt, a cationic polymer or a cati nic or nonionic surfactant reduced the malod r of the formulati ns sufficiently so that nly one half of the previ us c ncentration of fragrance was required, and light r, cleaner smelling fragrances could be utilized to enhance the smell of the formulations. The result has been formulations which are considerably more pleasant to the smell and which increase compliance.

EXAMPLE 25
REDUCED PUCKERING OF CONTAINERS

Previous unstabilized formulations when placed in high or low density polyethylene bottles would partially collapse the bottles. This is believed to have resulted from chemical reactions occuring between the formulations after it was freshly made and the gasses within the containers. During reaction with the compositions within the formulations the gasses within the containers were removed, thus decreasing pressure within the containers causing puckering. The stabilization which now occurs as a result of the use of reactive zinc salts, cationic polymers or cationic or nonionic surfactants has resulted in a cessation of the interaction between the formulations and the atmosphere within the bottles. No puckering occurs.

EXAMPLE 26
REDUCING PRECIPITATION

Certain unstabilized formulations, especially those comprised of high concentrations of protein and thioglycollate, develop a precipitate over time. This precipitate does not occur when zinc salts, cationic polymers and/or cationic or non-ionic surfactants are added to the formulations as described hereinabove.

WHAT IS CLAIMED IS:

1. A composition for treating keratinous tissue in mammals comprising:

a). from about 0.01% to about 25.0% by w ight of a film-forming protein;

b). about 0.1 to about 15% by weight of a compatible reducing agent;

c). at least about 0.05 weight percent of a reactiv zinc salt; and

d). at least one component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, oxidizing agents, coloring agents, perfuming agents and mixtures, thereof.

2. The composition according to claim 1 wherein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said keratinous tissue.

3. The composition according to claim 2 wherein said reactive zinc salt is selected from the group consisting of zinc oxide, zinc sulfocarbolate and mixtures thereof.

4. The composition according to claim 2 wherein said protein is keratin.

5. The composition according to claim 1 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

6. The composition according to claim 5 wherein said compatible reducing agent is thioglycollic acid or its salt.

7. The composition according to claim 2 wherein said oxidizing agent is selected from the group consisting of sodium perborate, sodium bromate and hydrogen peroxide in an amount ranging from about 0.01 to about 1.5% by weight of said composition.

8. The composition according to claim 1 further comprising an effective amount of a cationic polymer.

9. The composition according to claim 8 wherein said cationic polymer comprises about 0.01% to about 20% by weight of said composition and is a quaternary ammonium containing

polymer.

10. The composition according to claim 9 wh r in said polymer is a quaternary nitrogen-c ntaining cellul sic ether.

11. The composition according to claim 8 wh rein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said keratinous tissue.

12. The composition according to claim 11 wherein said protein is keratin.

13. The composition according to claim 11 wherein said compatible reducing agent is thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

14. The composition according to claim 13 wherein said oxidizing agent hydrogen peroxide and comprises about 0.01 to about 1.5% by weight of said composition.

15. The composition according to claim 1 or 9 further comprising about 0.05% to about 15% by weight of a surfactant selected from cationic and nonionic surfactants.

16. The composition according to claim 15 wherein said surfactant is a nonionic pyrrolidone containing surfactant substituted on the nitrogen of the pyrrolidone ring with a hydrophobic group selected from the group consisting of n-octyl, dodecyl, and coco and tallow alkyl groups.

17. The composition according to claim 15 wherein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said keratinous tissue.

18. The composition according to claim 17 wherein said reactive zinc salt is selected from the group consisting of zinc oxide and zinc sulfocarbolate and mixtures thereof.

19. The composition according to claim 18 wherein said protein is keratin.

20. The composition according to claim 17 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting f dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable

salts and mixtures thereof.

21. The compositi n according to claim 20 wherein said compatible reducing agent is thioglycollic acid or its salt.

22. The compositi n according t claim 15 further comprising a chelating agent.

23. The composition according to claim 22 wherein said chelating agent is included in amount equal to about 0.05 to about 2.0% by weight of said composition.

24. The composition according to claim 22 wherein said oxidizing agent comprises about 0.01 to about 1.5% by weight of said composition.

25. The composition according to claim 15 wherein said protein is keratin, said reducing agent is ammonium thioglycollate, said zinc salt is a mixture of zinc oxide and zinc sulfocarbolate, said surfactant is a pyrrolidone containing surfactant having an n-octyl group substituted on the nitrogen group of the pyrrolidone and wherein said composition further comprises hydrogen peroxide and ethylenediaminetetraacetic acid.

26. A composition for treating keratinous tissue in mammals comprising:

a). from about 0.01% to about 25.0% by weight of a film-forming protein;

b). about 0.1 to about 15% by weight of a compatible reducing agent;

c). an amount of a cationic polymer effective to substantially reduce the formation of malodorous side products; and

d). at least one component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, coloring agents, oxidizing agents, perfuming agents and mixtures thereof.

27. The composition according to claim 26 wherein said film-forming protein component is a protein containing sufficient cysteinyl residues to covalently bind to said tissue.

28. The composition according to claim 26 wher in said cationic p lymer is a quaternary ammonium containing polymer comprising at least about 0.01 w ight perc nt of said composition.

29. The composition according to claim 27 wherein said protein is keratin.

30. The composition according to claim 27 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

31. The composition according to claim 30 further comprising about 0.05% to about 15% by weight of a surfactant selected from the group consisting of cationic and nonionic surfactants.

32. The composition according to claim 31 wherein said surfactant is a nonionic pyrrolidone containing surfactant substituted on the nitrogen of the pyrrolidone ring with a hydrophobic group selected from the group consisting of n-octyl, dodecyl and coco and tallow alkyl groups.

33. The composition according to claim 32 wherein said film-forming protein component is a keratin.

34. The composition according to claim 33 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

35. A composition for treating keratinous tissue in mammals comprising:

a). from about 0.01% to about 25.0% by weight of a film-forming protein;

b). about 0.1 to about 15% by weight of a compatible reducing agent;

c). an amount of a surfactant selected from the group consisting of cationic and nonionic surfactants effective to substantially reduce the formation of malodorous side products; and

d). at least one component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, oxidizing agents, coloring agents, perfuming agents.

about 0.01% to about 25.0% by weight f said composition in solution t a thiol containing reducing agent comprising about 0.1% to about 15% by weight of said composition at a pH of at least about 9.0 in water or suitable solvent to produce an activated protein mixture;

b. dissolving at least one component selected from a reactive zinc salt, a cationic polymer and a surfactant selected from cationic and nonionic surfactants comprising at least about 0.05% by weight of said composition in said activated protein mixture.

45. The method according to claim 44 wherein said activated protein is exposed to an oxidizing agent in an amount equal to at least about 0.01 to about 1.5% by weight of said final composition after said exposing step a.

46. The method according to claim 44 wherein said activated protein is exposed to an oxidizing agent in an amount equal to at least about 0.01 to about 1.5% by weight of said final composition after said dissolving step b.

47. The method according to claim 44 wherein said activated protein mixture is first mixed with at least one component selected from water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, coloring agents and perfuming agents before said dissolving step b.

48. Compositions for use in treating the affects of aging skin including wrinkles and for promoting hair growth, nail growth and in stabilizing hair loss comprising:

a). from about 0.01% to about 25.0% by weight of a film-forming protein;

b) about 0.1 to about 15% by weight of a compatible reducing agent; and

c) the remainder of said composition comprising at least one further component selected from the group consisting of water, acids, bases, buffering agents, emulsifying agents, thickeners, solvents, preservatives, chelating agents, film-forming polymers, coloring agents, oxidizing agents, perfuming agents and mixtures, thereof.

49. The composition according to claim 48 wherein said oxidizing agent comprises about 0.01 to about 1.5% by weight.

50. The composition according to claim 48 wherein said oxidizing agent is hydrogen peroxide.

51. Th composition according to claim 48 wherein

36. The composition according to claim 35 wherein said surfactant comprises about 0.05% to about 15% by weight of said composition.

37. The composition according to claim 35 wherein said surfactant is a nonionic pyrrolidone containing surfactant substituted on the nitrogen of the pyrrolidone ring with a hydrophobic group selected from the group consisting of n-octyl, dodecyl and coco and tallow alkyl groups.

38. The composition according to claim 35 wherein said film-forming protein component is keratin.

39. The composition according to claim 35 wherein said compatible reducing agent is a thiol-containing reagent including agents selected from the group consisting of dithiothreitol, trithiohexitol, glutathione, cysteine, mercaptoethanol, thioglycerol, mercaptosuccinic acid, thiolactic acid, thioglycollic acid, their pharmaceutically acceptable salts and mixtures thereof.

40. The composition according to claim 39 wherein said compatible reducing agent is thioglycollic acid or its salt.

41. The composition according to claim 39 wherein said oxidizing agent is selected from the group consisting of sodium perborate, sodium bromate and hydrogen peroxide and comprises about 0.01 to about 1.5% by weight of said composition.

42. A method of treating normal and abnormal keratinous tissue to improve its condition, appearance, strength and promote its growth by contacting the tissue with any of the compositions from claims 1 through 41.

43. A method for treating conditions of keratinous tissue in mammals including wounds, abrasions, pressure sores, gingival erosion, sores and lesions of the oral cavity, corneal ulcers and abrasions, sebborhea, psoriasis, acne, acne scars, itching, callouses, corns, burns, miscellaneous rashes, non-specific dermatitis, eczematoid dermatitis, wrinkles, hang nails, chronic dermatitis, equine exuberant granuloma, decubitis ulcers, and canine cutaneous granulomas comprising applying to the effected area of the skin a composition comprising any of the compositions from claims 1 through 41.

44. A method for producing a composition for treating keratinous tissue comprising:

a. exposing a cysteinyl containing protein comprising

said film-forming protein is keratin.

52. The composition according to claim 48 wherein said reducing agent is thioglycollic acid or a salt of thioglycollic acid.

53. The composition according to claim 52 wherein said reducing agent comprises at least about 0.5 to about 10% by weight of said composition.

54. A method of cosmetically treating the affects of aging skin in mammals including wrinkles or promoting hair growth, nail growth and in stabilizing hair loss comprising applying any of the compositions from claims 1-41 to the skin or scalp of a subject to decrease wrinkles, decrease hair loss and promote hair growth.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/04649

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5):A61K 37/12,37/18,37/04,37/02,31/095,33/40,7/48,7/44

U.S. CL.: 514/2, 21, 859, 861, 863, 886, 887, 706, 557, 714, 974, 975; 424/543,641,642,76.21

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
U.S.	514/2, 21, 859, 861, 863, 886, 887, 706, 557, 714 974, 975; 424/543, 641, 642, 76.21

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

APS, CAS, BIOSIS

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 4,438,102 (GANCI), 20 March 1984, see the entire document.	1-54
Y	US, A, 3,842,848 (KARJALA), 22 October 1974, see the entire document.	1-54
X Y	GB, A, 2,160,419 (PURL), 24 December 1986, see the entire document	48-54 1-54
Y	Cosmetics and Toiletries, Vol. 92, 1977, Faucher et al., "Protection of the skin by a Cationic cellulose polymer", pages 39-43, see the entire document.	26-34,42-47
Y P	US, A, 4,909,986 (KOBAYASHI et al.) 20 March 1990, see the entire document.	26-34,42-47
Y P	US, A, 4,915,939 (IWAHASHI et al.), 10 April 1990, see column 1.	1-25,42-47
Y	Wilkinson et al., Harry's Cosmeticology, 7th ed., 1982, Chemical Publishing, New York, see pages 506-508.	35-47

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [9]

14 December 1990

Date of Mailing of this International Search Report [10]

06 FEB 1991

International Searching Authority [11]

ISA/US

Signature of Authorized Officer [12]

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